Imaging of Psycho-neuro-immune Interaction in Human

IV. 6. Imaging of Psycho-neuro-immune Interaction in Human

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Introduction

Interaction between psychological factors and bodily functions has been discussed for a long time. There may be positive and negative aspects in this interaction. Some mention immune enhancing effects of relaxation and imagery techniques[1,2] and exercise[3]. Others deal with high incidence of cancer and poor prognosis associated with certain psychological factors in cancer patients and so on[4,5,6]. Existence of psycho-neuro-immune interaction seems to be doubtless, but the mechanism would be complex. It has tended to be explained by involvement of the hypothalamic-pituitary-adrenal (HPA) axis. But this model seems to be lacking important components. Since psychosocial events must be "recognized" and "judged" in order that our consciousness feels them stressful, it seems that the model should include the cerebral cortex and limbic system. There might be a missing link between psychosocial events and body abnormal function of the HPA axis[7].

Previous animal studies demonstrated alteration of immune functions following selective destruction of brain structures such as the hypothalamus, cerebral cortex, and limbic system[8,9-12]. Recently, Wik and coworkers' honorable study demonstrated state-dependent correlation between cellular immune functions and the regional cerebral blood flow in normal human subjects by using ^{15}O-H_2O-PET[13]. Since the brain of cancer patients might be already affected by various causes, such as psychological, therapeutic and paraneoplastic factors, manifesting decreased regional glucose metabolism in the limbic system and the prefrontal cortex as demonstrated in our previous study, the result similar to that of Wik and coworkers' study could not be guaranteed[14]. It would be worthwhile examining comparable relationship in patients with cancer. Since psychological factors have been said to influence on prognosis of patients, research in this direction might give a useful information in explaining how the psychological factors determine physical conditions. The authors investigated the relationship between NKA, regional glucose metabolism and psychological scores in the brain of cancer patients.

Materials and Methods

Subjects were 8 cancer patients (mean age +/- s.d., 65 +/- 13, ranging 40 to 80, one woman and seven men) at various stages. They were admitted to the Hospital of Institute of Development, Aging and Cancer, Tohoku University. Their brain images were free from focal signs in MRI or CT. The study protocol was approved by the Ethics Committee for Clinical Research of Tohoku University and informed consent was obtained from each patient.

FDG was prepared using an automated synthesis system, and quality assurance tests were performed. Patients refrained from eating and drinking for at least 5 hours before the PET examination. The blood glucose level was measured before the injection of FDG. After injection of FDG, patients were requested to wait for 30 min, sitting quietly on a comfortable chair. PET examinations were performed using a SET2400W scanner (Shimadzu Inc., Kyoto, Japan) with the transaxial spatial resolution of 4 millimeter. The axial field of view of the scanner is 200-millimeter-long which was long enough to cover the whole brain in one scan. The brain was scanned about 60 min after injection (for 4 min) as a part of whole-body scan. Transmission scans were performed using a $^{68}Ge/^{68}Ga$ external rotating line source for tissue attenuation correction after emission scan[15].

PET images were reconstructed using a filtered-back projection (FBP) algorithm and were dead time- and decay- corrected. There was no significant patient movement or mis-positioning between transmission scan and emission scan. After reconstruction, brain images of the patients were extracted from the whole body images. The extracted brain images were spatially normalized by linear and non-linear transformations to minimize anatomical variation among patients, while preserving the regional metabolic activity using Statistical Parametric Mapping software package (SPM96)[16,17]. Statistics was applied on these image data at pixel-by-pixel basis. In the following analysis, all the pixel data were normalized to the group mean of the whole brain count of each patient (ANCOVA). Location of specific regions in the cancer patient group was represented in x, y, z coordinates and were identified in the stereotaxic coordinate human brain atlas[18].

Psychological status of each patient was evaluated using Zung's SDS[19-21] and Taylor's MAS[22,23] in Japanese translation[21,23].

NKA was measured as follows. The whole blood sample of 5 ml was taken from each patient just prior to injection of FDG. These samples were measured at Sumitomo Metal Bio-Science Inc. Laboratory (^{51}Cr Free Floating Method K-562 cell line kit was used with $Na_2{}^{51}CrO_4$ presented by Amersham Japan).

Results

Half of patients (4 out of 8) manifested decreased NKA compared with normal ranges (13-51: laboratory specific data). Mean score of MAS in cancer patients was 19.4+/-3.1, and SDS 35.6+/-6.9. Mean MAS was moderately elevated compared with normal

distribution measured with the Japanese version (14.3+/-7.8)[23]. Two patients were categorized as highly anxious (grade I), three patients as moderately anxious (grade II) and three patients (one female and two males) as mildly anxious (within normal range). For SDS, general distribution was identical to that of normal group (35+/-12)[21]. Only three patients belonged to the neurotic range (49+/-10), suggesting that they were possibly in mild mood disturbances.

Positive correlation was detected between NKA and MAS scores ($r = 0.96$, $p < 0.001$ by Pearson correlation test). No correlation was observed between patient age and psychological scores and between patient age and NKA.

According to SPM results, NKA correlated positively with rCMRglu in the left visual association cortex, left primary motor and premotor cortices, and right anterior cingulate gyrus. The NKA also correlated with the left primary sensorimotor cortex and left posterior parietal cortex but they did not survive Bonferroni correction (extent threshold:$p<0.4$), because of their small pixel cluster sizes. NKA correlated negatively in the right basolateral prefrontal cortex, right prefrontal cortex, orbitofrontal cortex, and inferoanterior temporal cortex (Figure 1 and Table 1).

Discussion

Links between psychosocial events and immune response have been studied well[24,25]. However, roles of cortical and limbic systems in psycho-immune responses have not been studied well yet. This response could be understood based on the fundamental framework as follows:

1) psychosocial behavior,
2) regional change in the brain, and
3) physiological changes (autonomic, endocrine and immune).

While there are enormous number of studies dealing with one or two dimensions introduced here, few study has been done taking all of the three dimensions into account because of its complexity. A functional brain imaging study might enable it.

Previous animal studies demonstrated altered immune functions following destruction of brain structures such as cerebral cortex, limbic system and brain stem[8-12]. Previous lesioning studies on the anterior hypothalamic area induced immune dysfunction in mice. Lesioning of the posterior hypothalamus gave rise to various results. Some studies suggested that destruction of the limbic structure induced enhancement of immune functions[8-12] and that lesioning of the cerebral cortex induced decreased immune function[10-12]. The purpose of these lesioning studies were to clarify the role of specific brain regions in the immune modulating interaction. Similar purpose could be accomplished in human non-invasively by using PET technique.

A recent work done by Wik and coworkers[13] demonstrated correlation between the regional cerebral blood flow (rCBF) and NKA and Concanavalin-A (Con A) response of lymphocytes in normal human subjects. This may be only one study available on this topic. They, after carefully excluding subjects with moderate to high anxiety, demonstrated that NKA correlated negatively with rCBF in the secondary somatosensory cortex whereas Con-A response correlated positively with rCBF bilaterally in the visual association, motor, sensory cortices, thalamus, putamen, and left hippocampus. Purpose of the present study was to see if a comparable trend can be detected in cancer patients. Naturally, patients built up moderate degree of anxiety or depression. To see a certain effect of emotional load on the immune consequences, anxious patients were not necessarily to be excluded. Curiously, our results looked opposing to that of NKA in Wik's study but seemed to be in accordance with that of Con-A study. Interpretation of this discrepancy is still unclear.

In the present study, at least it seemed that anxiety, NKA and metabolism in the cingulate and primary cortices correlated to each other. It seems to be relatively easy to explain the effects of imagery and exercise by possible close contact between immune cells and the visual and sensorimotor cortices, as demonstrated in the present study (Figure 1 and Table 1). However, anatomical connection between the two is unclear, and further interpretation is still difficult.

Combined with the results of lesioning studies on animals, the present result seems to demonstrate an antagonistic relationship between the cortical (including anterior cingulate gyrus) and limbic (including prefrontal cortex) systems concerning immunological consequences. In future, it could be expected that this approach will elucidate functional neuroanatomy of immune enhancing effects accompanied by relaxation, imagery and biofeedback techniques[1,2] and exercise[3] as well as psycho-biological mechanism of poor prognosis in cancer patients associated with certain psychological factors[4-6].

Conclusion

In spite of the small sample size, this observation might provide further support for the presence of interactions between the brain and immune system. The cerebral cortex and limbic system may take some important roles in psycho-neuro-immune-modulation. Functional brain mapping technique could produce reasonable results in investigating this interaction.

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Table 1. Regions of Linear Correlation to NKA.

Structure	Brodmann's Area	Hemi-Sphere	Talairach Coordinates Of statistical peak X	Y	Z	Z score of Statistical peak
(positive correlation)						
Visual association cortex	18	L	-32	-80	0	4.12
Anterior cingulate gyrus	32	R	12	26	40	3.60
Motor area	4/6	L	-45	-14	60	3.69
(negative correlation)						
Basolateral prefrontal cortex	47	R	36	46	-10	4.72
Prefrontal cortex	10	R	22	64	-2	4.41
Orbitofrontal cortex	11	L	-16	40	-16	3.86
Anterior temporal cortex	20	L	-26	12	-44	3.59

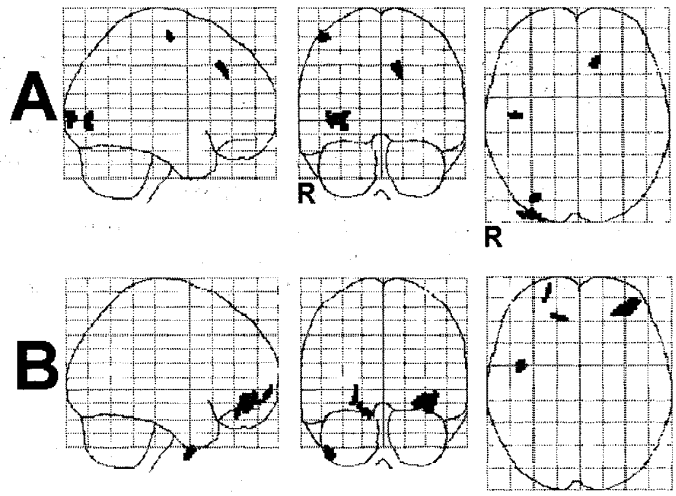

Figure 1. Regions Correlating with Natural Killer Cell Activity (NKA).A: positive correlation and B: negative correlation.Regions of significant correlation, denoted by black, are superimposed on MRI templates. (pixel height threshold $p<0.005$, extent threshold $p<0.4$ (43 voxel minimum).